REVIEW ARTICLE

Sinonasal Mucormycosis in a Tertiary Care Center: A Review of 30 Cases

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Abstract

Aim and objective: To report our experience in presentation, treatment, and outcome of rhino-orbito-cerebral mucormycosis in our institute.

Materials and methods: Retrospective, noncomparative analysis of medical records of 30 patients with mucormycosis seen over a period of 5 years.

Results: Data of 30 patients, 22 males and 8 females with a mean age of 47.3 (range 25–70 years), were analyzed. Total 25 patients had diabetes mellitus, 3 were post-renal transplant, and 2 were post-bone marrow transplant and on immunosuppressive drugs. Ophthalmic signs and symptoms were present in 12 patients, and intracranial involvement was present in 11 patients. Computed tomography/magnetic resonance imaging (CT/MRI) revealed involvement of paranasal sinuses in all patients. All were treated with amphotericin-B (3–7 g) and 29 patients underwent appropriate surgery. Posaconazole/caspofungin was started as adjuvant treatment in certain cases.

Conclusion: Mucormycosis is a rapidly spreading fungal disease with high mortality and demands immediate management without delay and generous debridement.

Keywords: Caspofungin, L. amphotericin-B, Posaconazole, Sinonasal mucormycosis.

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Introduction

Mucormycosis refers to a spectrum of diseases caused by infection with fungi in the order of Mucorales. Mucorales with seven genera, *Rhizopus, Mucor, Absidia, Saksenaea, Rhizomucor*, *Apophysomyces*, and *Cunninghamella*, are documented to be pathogenic organisms that produce invasive disease in humans, with the most common causative agent being of the *Rhizopus* species. Endemic worldwide, Mucorales are predominantly saprophytic organisms found on decaying organic material. However, these organisms also act as opportunistic pathogens causing an acute angioinvasive infection seen primarily in the immunocompromised.[1] Patients on immunosuppressive drugs such as steroids, patients with immunodeficiency disorders such as aplastic anemia, neutropenia, acquired immune deficiency syndrome, malnutrition, hematologic malignancy, dialysis patients on desferoxamine, and organ transplant patients are also at risk of infection by the fungi.

Patients with poorly controlled diabetes and ketoacidosis are at high risk of developing rhinocerebral mucormycosis, with systemic acidosis creating an ideal environment for the growth of *Rhizopus*. However, initial presentation of rhinocerebral mucormycosis infection can often appear nonspecific, making correct diagnosis extremely difficult until the disease has caused significant morbidity, aggressive fungal invasion of the paranasal sinuses, orbit, hard palate, and brain.[2,3]

Materials and Methods

Records of 30 patients with a diagnosis of mucormycosis admitted to our hospital from January 2010 to March 2015 were reviewed. Their ages ranged from 25 to 70 years with a mean (SD) of 47.3 (14.4) years. Patients having smear and/or histopathological evidence of mucormycosis only were included. The study was approved by the institute's ethics committee. Four patients with diabetes were on insulin, with 11 on oral hypoglycemic drugs. Their clinical, biochemical, radiological (computed tomography/magnetic resonance imaging), and treatment profiles (amphotericin-B/posaconazole/caspofungin and appropriate surgical intervention) were recorded in a special datasheet and analyzed.

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Results

Total 25 patients had diabetes, 10 of which were previously undiagnosed. Five patients had diabetic ketoacidosis. Three patients were post-renal transplant for chronic renal failure, two patients were post-bone marrow transplant for aplastic anemia. Diagnosis of mucormycosis is based on direct microscopy of aspirate/crusts from the nasal/sinus mucosa in 25 and on histopathology in 5. The finding of aseptate hyphae with right-angled branching was considered pathognomonic for determining the morphology of *Mucor*. On CT/MRI, all patients had evidence of paranasal sinuses involvement. The ethmoid (86%) and maxillary sinuses (80%) were most commonly involved, followed by sphenoid and frontal sinus in six (20%) each and pansinusitis in five (16.6%) (Fig. 1). Features of

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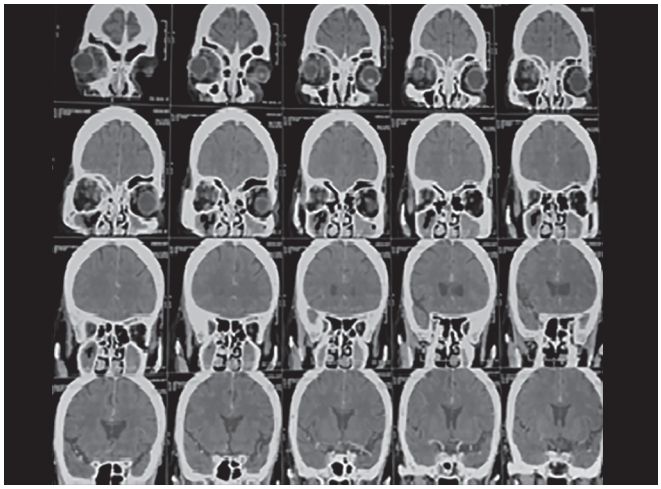

Fig. 1: Computed tomography showing pansinusitis involvement

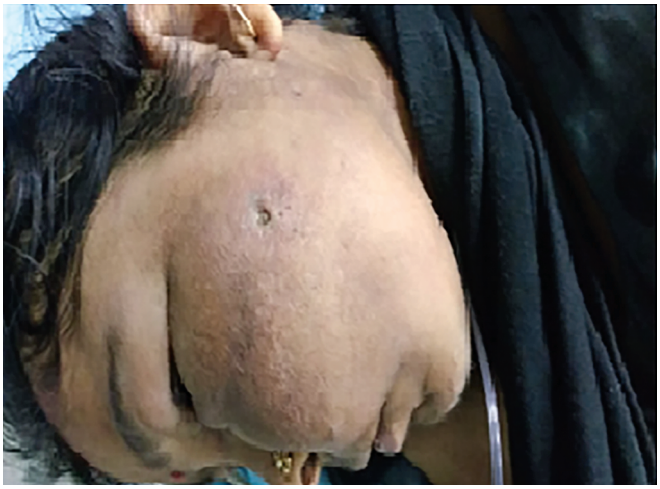

Fig. 2: Facial edema/necrosis

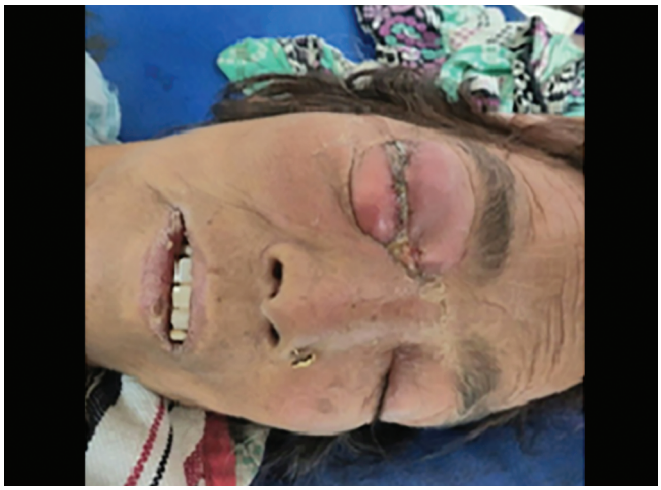

Fig. 3: Orbital involvement

Table 1: Frequency of signs and symptoms

Signs and symptoms	*Frequency*
Nasal discharge/crusting	25
Facial swelling/necrosis	10
Altered sensorium	5
Palatal ulcer/necrosis	15
Pain	30
Hemiparesis/meningeal signs	3
Ophthalmoplegia	8
Proptosis/chemosis	7
Periorbital swelling	12
Loss of vision	5

rhino-orbito-cerebral mucormycosis were present in 11 cases, five developed it during the hospital stay.

Facial swelling/necrosis was seen in 10 patients (Fig. 2). Orbital involvement was observed in 12 patients (Fig. 3) and no perception of light was seen in 5 patients requiring orbital exenteration. Cavernous sinus thrombosis present in eight patients. Intracranial extension with cerebral lobe involvement presenting as hypodense/hypointense area with or without rim enhancement was observed in three patients. One of these patients had a massive cerebral infarct. The management protocol involved control of the predisposing factors, aggressive surgical debridement, systematic administration, and local irrigation with antifungal therapy. All of these patients started on amphotericin-B. All except one with extensive intracranial involvement on presentation underwent surgical debridement. All these were treated with amphotericin-B, with total doses varying from 3.0 to 3.5 g, and 29 patients were subjected to appropriate surgery including lateral rhinotomy, sinusectomy, orbital exenteration, and maxillectomy. Five of these patients developed impairment of renal function with amphotericin-B treatment, which was reversible on withholding the drug for few days. We chose the addition of caspofungin/posaconazole as rescue therapy. Despite the lack of *in vitro* susceptibility of Mucorales to echinocandins, there are preclinical studies and a small retrospective study in which the success rate treating rhino-orbito-cerebral mucormycosis is higher with a combination of polyene–caspofungin.[4] For prolonged treatment, we chose oral posaconazole. The European guidelines strongly recommend posaconazole for salvage therapy (Tables 1 and 2).[5]

Discussion

Mucormycosis has various clinical presentations; rhino-sino-orbital and rhinocerebral mucormycosis are the most common. Rhinocerebral mucormycosis causes a very high residual morbidity and mortality due to the angioinvasive property of the fungus, thereby causing vascular occlusion and consequently resulting in extensive tissue necrosis.[6] Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-orbital region cautions for early diagnosis and aggressive management in these patients. Mucormycosis typically originates in the nasal or oral mucosa, spreads to the paranasal sinuses, and enters the orbit via the ethmoid and maxillary sinuses or via the nasolacrimal duct.[7] Intracerebral extension may occur from the orbit via orbital apex, orbital vessels, or via cribriform plate.[7] A black necrotic eschar is the most typical lesion, but its absence does not rule out the disease. Initial symptoms are usually those of a sinusitis preseptal or orbital cellulitis. Reversal of predisposing conditions is strongly recommended, i.e., using granulocyte colony-stimulating factor in hematological patients with ongoing neutropenia, controlling hyperglycemia and

Table 2: Disease profile

Total no. of patients	30
Comorbidities	
Diabetes	25
Post-renal transplant	3
Post-bone marrow transplant	2
Onset of symptoms to presentation (days)	
1–5	15
5–10	10
>10	5
Extent of disease	
Limited to sinus	7
Sino-orbital	12
Sino-orbito-cerebral	11
Treatment	
Surgery + L. amphotericin-B,	20
L. amphotericin-B,	1
Surgery + L. amphotericin-B, + posaconazole	5
Surgery + L. amphotericin-B, + caspofungin	4
Outcome (survival)	
Limited to sinus	7/7
Sino-orbital	10/12
Sino-orbito-cerebral	1/11

ketoacidosis in diabetic patients, and limiting glucocorticosteroids to the minimum dose required.

Preoperative contrast-enhanced CT is useful in defining the extent of the disease. Scans show the edematous mucosa, fluid filling the ethmoid sinuses, and destruction of periorbital tissues and bony margins. Although sinus CT is the preferred imaging modality, bony destruction is often seen only late in the course of the disease after soft tissue necrosis has already occurred.[8] Magnetic resonance imaging is useful in identifying the intradural and intracranial extent of the disease, cavernous sinus thrombosis, or thrombosis of the cavernous portion of the internal carotid artery. However, patients with early mucormycosis may have normal MRI and CT scans and surgical exploration with biopsy of the areas of suspected infection should always be performed in high-risk patients. Therapy guidelines have been recently published.[5] Duration of therapy is an important issue, given the expense of antifungal treatment. Extensive surgical debridement is difficult to achieve because important structures are often adjacent to necrotic tissues, particularly in sinonasal, rhino-orbital, and, especially, cerebral involvement. European guidelines state "continue treatment until complete response (on imaging) and permanent reversal of immunosuppression are achieved" but no prospective studies have been performed.[5]

Conclusion

Factors associated with poor survival are: (1) intracranial extension, (2) increased lag time, and (3) extensive facial necrosis. Extensive orbital involvement by Mucorales required orbital exenteration in five patients. One patient with intracranial extension survived. Treatment with posaconazole and caspofungin was started as a rescue therapy in advanced diseases having poorer prognosis, so their effect in treatment outcome cannot be commented upon and further larger studies required in this perspective.

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